BMJ Open

Cohort Profile: GendAge and Berlin Aging Study II (BASE-II)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-045576
Article Type:	Cohort profile
Date Submitted by the Author:	05-Oct-2020
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Keywords:	GENERAL MEDICINE (see Internal Medicine), GERIATRIC MEDICINE, PUBLIC HEALTH, VASCULAR MEDICINE

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Cohort Profile: GendAge and Berlin Aging Study II (BASE-II)

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Keywords: GendAge, Berlin Aging Study II, BASE-II

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Abstract

Purpose: The study “Sex- and gender-sensitive prevention of cardiovascular and metabolic disease in older adults in Germany”, the GendAge study, focusses on major risk factors for cardiovascular and metabolic diseases and on the development of major outcomes from intermediate phenotypes in the context of biological sex and gender differences. It is based on a re-investigation of participants of the Berlin Aging Study II (BASE-II).

Participants: The BASE-II follow-up assessments took place between 22 June 2018 and 10 March 2020 in the context of the GendAge study. A total of 1,100 participants (older BASE-II group) with baseline data assessed at least by one of the BASE-II partner sites were investigated in the follow-up. Of these 1,083 participants have been medically assessed at baseline, which had a mean age of 75.60 years (SD ± 3.77, range 64.91 - 94.07 years) in the current assessment, with up to 10.37 years of follow-up (mean follow-up at 7.35 years, SD ± 1.46).

Findings to date: In GendAge, we have developed a retrospective gender score taking BASE-II baseline data reflecting sociocultural aspects into account. This gender score was associated with a number of clinical and psychosocial variables and performed better in predicting differences in a subset of variables compared to biological sex.

Future plans: The gender questionnaire implemented as part of the follow-up assessments described here will allow to re-calculate the gender score on a far more comprehensive dataset and its evaluation based on the newly collected clinical and psychocial follow-up data. At the same time, the other BASE-II research foci established over the past 10 years will be continued and strengthened by the transition of BASE-II into a longitudinal study.

Registration: GendAge is registered in the German Clinical Trials Register (Study-ID: DRKS00016157).

Strengths and limitations of this study

- The GendAge study focusses on major risk factors for cardiovascular and metabolic diseases and on the development of major outcomes from intermediate phenotypes in the context of biological sex and gender differences
- The BASE-II follow-up assessments of 1,100 men and women aged 65–94 years in 2018–2020 were part of GendAge
- The Berlin Aging Study II (BASE-II) is aiming at identifying factors that distinguish ‘healthy’ from ‘unhealthy’ ageing and completed baseline assessments in 2,200 adult volunteers (1,600 participants aged 60-80 years and 600 participants aged 20-35 years) in 2014.
- In addition to re-assessing most baseline measures (geriatrics, internal medicine, immunology and psychology) we implemented a comprehensive gender questionnaire covering socio-cultural gender characteristics and added high-quality echocardiography
- The possibility of a selection bias in the follow-up study population is a limitation, which we have made various efforts to counteract

Introduction

The original BASE-II cohort

The Berlin Aging Study II (BASE-II) was launched as a multidisciplinary study aiming at identifying factors that distinguish 'healthy' from 'unhealthy' ageing. Baseline recruitment of 2,200 adult volunteers from the Berlin metropolitan area and baseline assessments were completed in 2014 [1]. The ascertainment protocol included the collection of data from different domains for each of the 1,600 participants aged 60-80 years and 600 participants aged 20-35 years, namely geriatrics and internal medicine, immunology, genetics, psychology, sociology, and economics [1,2].

BASE-II baseline data were used in a multitude of analysis projects focusing on key questions revolving around age and aging. Research topics of the ongoing study include, but are not limited to, cognitive aging [3-5], cardiovascular and metabolic health [6-8], sarcopenia and frailty [9,10], psychosocial factors of aging [11,12], genetic risk factors of aging and disease [13-15], the impact of characteristics of the neighborhood people are living in [16], as well as indicators of biological age [17,18] and immune biomarkers [19]. For an overview of the BASE-II research foci and publications, refer to [20] and the BASE-II website (https://www.base2.mpg.de/en/project-information/publications).

What is the reason for the new data collection?

The study "Sex- and gender-sensitive prevention of cardiovascular and metabolic disease in older adults in Germany", the GendAge study, focusses on major risk factors for cardiovascular and metabolic diseases and on the development of major outcomes from intermediate phenotypes in the context of biological sex and gender differences. Major outcomes include but are not limited to myocardial infarction (MI), heart failure (HF) and T2D, as well as mortality and quality of life. Major aim is the first systematic collection of follow-up data in BASE-II participants and the analysis of sex- and gender-related differences. Gender was obtained by

a novel comprehensive gender questionnaire covering a range of socio-cultural gender characteristics as a central instrument. This questionnaire contains an adapted version of the gender questionnaire developed by Pelletier and colleagues [21] and additionally included the variables used to calculate a gender score retrospectively by making use of gender-related variables assessed at baseline [22]. This gender questionnaire will be central to develop a second gender score (GS-II). [23].

What will be the new areas of research?

There is new knowledge showing that sex differences play a role in all major diseases, their prevention and treatment [24]. Other studies showed that gender as the sociocultural dimension of disease affects disease and treatment outcomes and also well-being [21,25]. The new areas of research cover the systemic inclusion of sex-specific analysis and the inclusion of gender. Aging interacts with sex and gender differences in health, but it is not clear, which mechanisms are most important.

GendAge aims to better understand, which mechanisms affect cardio-metabolic morbidity, mortality, and quality of life among older adults in a sex- and gender-sensitive manner.

While on different occasions follow-up data were ascertained for questionnaire and cognitive data [5,26-30], as being part of the GendAge study this cohort profile update describes, the first comprehensive follow-up assessments in BASE-II that also includes a re-assessment of central variables in the areas of internal medicine and geriatrics. At the same time, the other BASE-II research foci established over the past 10 years as described above (and in [20]) will be continued and strengthened by the transition of BASE-II into a longitudinal study.

Cohort description

The original BASE-II sample consisted of 2,200 participants from the greater metropolitan area of Berlin, Germany (baseline assessment between 2009 and 2014). The follow-up assessments within the GendAge study took place between 22 June 2018 and 10 March 2020 at the Charité Universitaetsmedizin Berlin. During the recruitment of the follow-up cohort, we approached all participants of the remaining pool of 1,428 subjects out of the originally 1,671 subjects who completed the baseline medical assessments at an age of 60 years and older. Potential follow-up participants were contacted via telephone and an invitation letter containing the comprehensive participant's information sheet and the letter of consent was sent at least five days before the scheduled first of two assessment days to all subjects who agreed to participate at least five days before the scheduled first of two assessment days. Additionally, we included 17 subjects of the older age group who were not medically assessed at baseline, but were part of the BASE-II sample with data collected from at least one of the BASE-II partner sites. As presented in the flow chart (Figure 1), this resulted in a total of 1,100 participants of the older BASE-II group investigated in the follow-up. These older participants had a mean age of 75.60 years (SD ± 3.77, range 64.91 - 94.07 years), with up to 10.37 years of follow-up (N=1,083, mean follow-up at 7.35 years, (SD ± 1.46), range 3.91 - 10.37). At baseline, the BASE-II included a group of 600 younger subjects aged 20-35 years serving as a reference population [1], of which 500 completed baseline medical assessments. Between 7 February 2020 and 13 March 2020, we performed follow-up assessments in a total of 64 participants of this younger group until these assessments were suspended because of the SARS-Cov2 pandemic. These younger participants had a mean age of 36.81 years (SD ± 3.46, range 29.32 - 44.05 years), with up to 10.7 years of follow-up (minimum 6.08 years, mean follow-up at 8.16 years, SD ± 1.58).

Findings to date

At follow-up, almost all of the older participants were retired (97.3%) as compared with 86% at the time of baseline assessment. At baseline, BASE-II participants were characterized by higher education and better self-reported health status than the general population of Berlin and Germany [1]. At follow-up, this selection seems to have increased, with 68.8% of the participants reported to have a high school degree (51% at baseline) and about 61% rated their health as *very good* or *good* (40% at baseline). The rate of divorce had been above average at baseline with 29% and had dropped to 21.7% at follow-up, which is still significantly above the German and Berlin average (i.e. 12.0% and 17.4%, respectively)[31], while the proportion of widowed participants increased from 5% at baseline to 10.5% in the follow-up dataset of older BASE-II participants. As shown in Table 1, differences between men and women are evident with respect to the sociodemographic status and psychosocial functioning in the follow-up cohort: Men reported significantly higher school degrees and higher satisfaction with life in general than women. Interestingly, self-rated health did not differ between men and women, which matches to the overall morbidity estimated by an adapted version of the Charlson morbidity index [17,32], which also did not differ between men and woman ($p=0.981$, Table 1). This morbidity index, however, increased between baseline and follow-up ($p<0.001$, Wilcoxon signed-rank test and data not shown). Differences between men and women exist in the follow-up dataset with respect to the prevalence of some, but not all cardiovascular risk factors and diseases (Table 1). Men for example had a higher BMI and a higher proportion of men reported to have T2D and myocardial infarction than women. No significant differences between men and women were evident in the reporting of hypertension, peripheral artery disease, and stroke. With the aim of achieving a particularly high quality standard in the assessment of participant's medical history at baseline and follow-up, including past and current diseases, the information given by the participants was recorded from study physicians as part of a structured one-to-one interview, allowing to consider its plausibility. This, however, does not cover the gap between reported (anamnestic) diseases and the

diseases diagnosed in the course of the study. This is exemplified by T2D, which was reported by 15.6% and 8.8% of men and women, respectively. In contrast, this disease was diagnosed in 20.7% of men and 13.3% of women based on the ESC criteria 2019 [33], indicating that a substantial proportion of almost 30% was unaware of the disease (Table1).

With the aim of investigating human ageing processes in BASE-II under consideration of different disciplines and longitudinally, the baseline investigation aimed at the most comprehensive data collection possible. At follow-up, most of these data in the field of geriatrics, internal medicine and psychology were again part of the study protocol (for a select overview, see Table 2). As the follow-up assessment being part of the GendAge study, we have implemented a comprehensive gender questionnaire covering a range of socio-cultural *gender* characteristics as a central instrument. This questionnaire contains an adapted version of the gender questionnaire developed by Pelletier and colleagues [21] and additionally included the variables used to calculate a gender score retrospectively by making use of gender-related variables assessed at baseline [22]. This gender questionnaire will be central to develop a second gender score (GS-II) and to reach the GendAge goals.

With a focus on cardio-metabolic diseases in GendAge, we extended the broad range of data assessed in this area at baseline by echocardiography. Data on right and left ventricular and atrial morphology and systolic and diastolic function and vascular stiffness were obtained by a trained investigator (US) on a General Electric Vivid T8 R3 System and analyzed by a trained analyst (ET). 10% of echo analysis were controlled by an independent supervisor. The intraclass correlation coefficient (ICC) between analyst and independent supervisor was 0.87 (LV IVSd: 0.86, LVEDV Biplane: 0.95, LVEF Biplane: 0.87, E/A: 093). LVEF was higher in women than in men, in agreement with most recent publications, and probably partially due to higher rate of MI in men[34].

Peripheral blood mononuclear cells were prepared from 903 participants at follow-up and frequencies as well as absolute counts of recent thymic emigrants (RTEs), T_{EMRA} effector T cell subsets (T_{EMRA}) and cytotoxic $CD4^+$ T cells were directly assessed. While RTEs are known to

decrease with ageing [35], alterations in T_{EMRA} and specialised cytotoxic $CD4^+$ T cell compartments can be indicative of age-related perturbations of systemic T cell immunity [36]. The immunological screening has so far revealed significantly higher frequencies of RTEs in women as compared to men, indicating a higher thymic T cell production even at the advanced ages of the GendAge participants. In men, more $CD45RA^+$ re-expressing TEMRAs were detected than in women (Table 1). These cells are associated with chronic viral infections (e.g. CMV) and can serve as a signature of immune-senescence [37]. We found no significant difference in the frequencies of cytotoxic $CD4^+$ T cells. Together, these preliminary findings confirm the better immune status of aged women as compared to men. A detailed analysis of the datasets will identify additional correlates of sex and gender, aging, and the immune system.

Other measurements

Similar to baseline, we determined numerous routine laboratory parameters from blood and urine (Table 2), and also stored blood plasma/serum and urine samples for future analyses. Genomic DNA was already extracted from EDTA-blood and buccal swab samples from GendAge participants, which will be used e.g. for the profiling of genome-wide DNA methylation signatures and new genome-wide single nucleotide polymorphism genotyping experiments (Table 2). In-between the two assessment days at the Charité, participants were asked to fill out a comprehensive psychosocial take-home questionnaire and return this at their second Charité visit. Moreover, another wave of cognitive assessments (see Table 2) carried out by the Max Planck Institute for Human Development (MPIB) has been tightly linked to the GendAge assessment of BASE-II participants. The cognitive session (= third study visit) was followed 7 days after the second medical examination and lasted about 4.5 to 5 hours. Subjects were tested in groups of 4–6 individuals. The cognitive battery included 17 measures of learning and memory performance, attention/processing speed, working memory, executive functioning, and perceptual speed (see Table 2). Within the week between study visit 2

(Charité) and 3 (MPIB) accelerometers (ActiGraph wGT3X-BT) have been used to track participants' physical activity and sleep in a subset of our participants (N=750).

After the cognitive session, participants were invited to take part in a one-to-one interview on a different day. This additional individual assessment took up to 60 minutes and serves as a cohort comparison between the BASE and BASE-II study populations. This additional data collection will also contribute to the BASE-II cognitive waves, allowing us to further investigate individual differences in aging trajectories (for an overview, refer to[20]).

Furthermore, and as part of a collaboration with the Lifebrain study, a consortium of European studies funded by the EU Horizon 2020 Framework Programme[38], we collected blood samples using dried blood cards, in order to determine laboratory parameters with identical methods used for all Lifebrain participating sites. Lifebrain aims at identifying determinants of healthy lifespan development by integrating and harmonizing data and results from 11 large and predominantly longitudinal European samples from 7 countries. This has yielded a database of fine-grained measures focusing on brain and cognition from more than 7,000 individual participants.

The GendAge study was approved by the Ethics Committee of the Charité–Universitätsmedizin Berlin (approval number EA2/144/16) and all participants gave written informed consent. GendAge is registered in the German Clinical Trials Register (Study-ID: DRKS00016157). The cognitive battery was approved by the Ethics Committee of the Max-Planck-Institute and the genomics experiments were approved by the Ethics Committees of the Charité (approval number EA2/144/16) and the University of Lübeck (approval numbers AZ19-390A and 19-391A).

Strengths and limitations

The BASE-II follow-up assessments covered most of the medical, psycho-social and cognitive domains and variables assessed at baseline, and thereby taking the BASE-II characteristic of an exceptionally broad and in-depth data collection to a next, longitudinal level. In addition, and in the context of the GendAge focus on cardio-metabolic disease, we extended the assessments in this area e.g. by including high-quality echocardiography resulting in a unique data collection. This strength with respect to comprehensive and longitudinal data offers the potential to answer a number of questions that are of crucial relevance for the health of old women and men. Thus, GendAge will make important contributions for improvements in understanding the health and well-being of older adults in both genders. BASE-II was initiated as a multidisciplinary study with expertise in a broad range of fields relevant for aging research (e.g. internal medicine and geriatrics, biology, psychology, genetics, immunology, socio-economics, and now in GendAge further extended by socio-cultural aspects of gender). The past ten years of BASE-II research have shown that multidisciplinary collaboration is not only a statement of intent, but a fruit-bearing working posture and a clear strength of BASE-II.

Sampling bias is a challenge which cohort studies have to deal with, and this is especially an issue in the follow-up of older study populations such as the older group of BASE-II participants. To address this, we have made a considerable effort (e.g. offering a taxi service for participants not able to travel independently) to include as many participants in the follow-up as possible. Additionally, and similar to baseline, we are able to systematically quantify the sampling bias and even account for it when it comes to the question of generalizability of study results to a population as a whole (e.g., Berlin or Germany), due to the evaluation of selectivity and representativeness via the German Socio-Economic Panel Study (SOEP) [1]. Despite these possibilities we cannot rule out the possibility of a selection bias completely, which certainly is a weakness of this study, a weakness that applies to all cohort studies relying on voluntary participants who have been non-randomly recruited. With our direct

comparability to the national representative SOEP study, we are in a position though to quantify the amount of selectivity and, if need, take measures to correct and adjust our results.

Collaboration

More details on GendAge can be found at https://gendage.charite.de/en/ and information on the BASE-II as a whole is available at https://www.base2.mpg.de/en. BASE-II has a tradition of sharing data and biobank samples in joint collaborative projects which will be continued with respect to BASE-II data assessed in GendAge. Interested groups are invited to contact the study coordinating PI Ilja Demuth at ilja.demuth@charite.de for the data-sharing application form. Each application will be reviewed by the GendAge PIs (currently ID, VRZ and DG) and the decision communicated to the applicants usually within 4 weeks of submission.

Participant and public involvement

Participants and public were not involved in the design or conduct of this study.

Funding statement

The GendAge study research project (Co-PIs are Ilja Demuth, Vera Regitz-Zagrosek, and Denis Gerstorf) is supported by the German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung, BMBF) grant numbers 01GL1716A (ID and VRZ) and 01GL1716B (DG). Genomics assessments are funded by the Cure Alzheimer's Fund (as part of the "CIRCUITS-AD" consortium project) and the European Research Council's "Horizon2020" funding scheme (as part of the "Lifebrain" consortium project; both to LB). Additional contributions (e.g., equipment, logistics, personnel) are made from each of the participating sites.

Contributorship statement

Conceived and designed the study: ID, VRZ, SD, UL and DG. Collected study specific data: I.D., VLB, JD, SD, US, DS, ET, JB, LB and AT. Analysed the data: ID, ET and JB. Wrote the manuscript: ID. All authors revised and approved the manuscript.

Acknowledgements

We are deeply indebted to all individuals of the BASE-II cohort who have agreed to participate in the follow-up assessments. We would further like to thank all staff members and students involved in the medical examinations of participants and documentation, especially Nora Berger, Janina Dombrowski, Mergim Domuzeti, Elisa Dreißig, Ilona Enarovic, Anthony Ganswindt, Thomas Grenkowitz, Anna Hunold, Ilias Katsianas, Yoo-Ri Kim, Jörn Kiselev, Paula Krull, Christine Kytmannow, Elisa Lemke, Julia Mätzkow, Charlotte Mentzel,

Nadja Mielke, Narantuya Mishig, Angela Motz, Eduard Nitschke, Aabi Okute, Danai Pantelakis, Sophie Poser, Johanne Spieker and Taleka Vollmar (all Charité Universitaetsmedizin Berlin, Biology of Aging group); and Luisa Lüth, Mariebelle Kaus, Isabel Ganter, Marlene Rosendahl, Jasmin Boneberger, Antonia Sprenger, Hania El-Kersh (all Humbold University, Department of Psychology), and Kirsten Becker for the excellent daily organization of the running study within and between the research units, the Telefonstudio for their daily contact with the participants, Martin Becker for the continuous quality checks of our sample and Berndt Wischnewski for updating the database and cognitive battery (all Max Planck Institute for Human Development).

We kindly acknowledge the excellent cooperation with the Central Biomaterial Bank, the joint core facility of the Charité-Universitätsmedizin Berlin and the Berlin Institute for Health (BIH). Furthermore, we appreciate the great support by the BIH-REDCap team and especially from Andreas Hetey.

Conflict of interest: None declared.

Tables

Table 1: Selection of BASE-II follow-up characteristics as assessed of the GendAge study – older group of participants

	Total number of observations	Women[1] (N=573, 52.1%)	Men[1] (N=527, 47.9%)	*p-value*[2]
Age (years)	1,100	75.7 (± 3.5)	75.5 (± 4.0)	0.276
Highest school degree Elementary school Intermediate school High school	1,095	35 (6.1%) 183 (32.0%) 354 (61.9%)	18 (3.4%) 104 (19.9%) 401 (76.7%)	8.4×10^{-7}
Family status Married Not married, in partnership Single Divorced Widowed Other	1,098	218 (38.0%) 12 (2.1%) 60 (10.5%) 187 (32.6) 89 (15.5%) 7 (1.2%)	386 (73.5%) 19 (3.6%) 33 (6.3%) 51 (9,7%) 26 (5.0%) 10 (1.9)	3.0×10^{-34}
Employment status Retired	1,055	540 (97.6)	486 (96.8)	0.689
Self-rated health Very good Good Fair Poor or very poor	1,096	56 (9.8%) 284 (49.7%) 166 (29.0%) 66 (11.5%)	65 (12.4%) 262 (50.0%) 143 (27.3%) 54 (10.3%)	0.499
Satisfaction with life in general	1,097	7.9 (±1.6)	8.1 (±1.4)	0.034
Digit Symbol Substitution Test[3]	1,095	41.82(±8.28)	39.65(±8.95)	3.4×10^{-5}
Depression (ever diagnosed)	1,095	122 (21.3%)	63 (12.0%)	5×10^{-5}
BMI	1,098	26.6 (±4.7)	27.4 (±3.7)	0.005
Diabetes mellitus type II (self-reported)	1,097	49 (8.6%)	82 (15.6%)	3.7×10^{-4}
Diabetes mellitus type II (diagnosed/ ESC criteria 2019)	1,097	76 (13.3%)	109 (20.7%)	0.001
Metabolic Syndrome (diagnosed, AHA/IDF/NHLBI criteria 2009)	1,074	252 (45.5%)	327 (62.9%)	1.2×10^{-8}
Hypertension	1,097	296 (51.7%)	311 (59.2%)	0.013
Myocardial infarction	1,097	11 (1.9%)	24 (4.6%)	0.015
Stroke	1,096	13 (2.3%)	20 (3.8%)	0.158
Peripheral artery disease	1,094	8 (1.4%)	15 (2.9%)	0.138
Morbidity index	955	1.0 (IQR 2.0)	1.0 (IQR 2.0)	0.594
Pulse wave velocity (m/s)	932	11.21 (±0.92)	11.04 (±0.91)	0.006
Left ventricular ejection fraction (%)	774	64.16 (±6.42)	62.90 (±5.75)	0.004

Frailty (Fried) Not frail Pre-frail Frail	1,087	260 (45.4%) 280 (48.9%) 28 (4.9%)	251 (47.6%) 248 (47.1%) 20 (3,8%)	0.542
Maximal hand grip strength (kg)	1,098	20.5 (±4.4)	35.1 (±6.8)	3.1×10^{-236}
Recent thymic emigrants (naïve CD4⁺ T cells)	395[3]	64.69 (± 16.34)	51.03 (± 13.69)	$6.3x10^{-16}$
T_{EMRA} (effector memory T cells re-expressing CD45RA)	395[4]	32.82 (± 19.96)	34.94 (± 21.29)	0.309
Cytotoxic SLAMF7+ CD4⁺ T cells	181[5]	6.02 (± 5.98)	6.05 (± 6.60)	0.974

[1]Data are presented as N (%), mean ±standard deviation or median (interquartile range, IQR). [2]Differences between women and men were assessed using the parametric t test, the nonparametric Mann-Whitney U test or the χ2 where appropriate. [3]assessed at study visit 1 [4]903 expected to be available after completion of the analyses. [5]700 expected to be available after completion of the analyses.

Table 2: BASE-II follow-up assessments during the three study visits in the GendAge study

Type of assessment/ domain	Example assessments/tests
Physical examination and medical history	Medical history structured by organ systems, medication, body weight, height, lifestyle (including smoking status, alcohol consumption, physical activity)
Physical status and functional tests	Tinetti Mobility Test, Timed up & Go Test, Barthel Index (ADL), Lawton Instrumental Activities of Daily Living Scale (IADL), hand grip strength, anthropometric parameters, pulse wave velocity/ arterial stiffness (Mobil-o-Graph), echocardiography, electrocardiography (ECG), spirometry, motion monitoring (Actigraph), dual-energy X-ray absorptiometry (DXA)[1],
Psychological screening tests	Mini Mental State Examination (MMSE), Digit Symbol Substitution Test (DSST)[2], Center for Epidemiologic Studies Depression Scale (CESD)
Questionnaires	EPIC (food-frequency questionnaire), Gender Questionnaire, Pittsburgh Sleep Quality Index, Rapid Assessment of Physical Activity, SARC-F , SF-36
Laboratory values[3]	Blood, serum or plasma: 25-hydroxyvitamin D, apolipoprotein A1, apolipoprotein B, basophiles, calcium, cortisol, creatinine, creatinine kinase, C-reactive protein, cystatin C, dehydroepiandrosterone, eosinophils, erythrozytes, ferritin, folic acid, gamma-glutamyltransferase, glucose 1, glucose 2[4], glutamate, oxalacetate transaminase, glutamate-pyruvate transaminase, HbA1c, HDL-cholesterol, hematocrit, hemoglobin, homocysteine, international normalized ratio, iron, LDL-

	cholesterol, leukocytes, lipoprotein (a), lymphocytes, magnesium, MCH, MCHC, MCV, monocytes, neutrophils, oestradiol, osteocalcin, partial thromboplastin time, RDW, sex hormone-binding globulin, testosterone, thrombocytes, thyroid-stimulating hormone, thyroxine, total-cholesterol, triglycerides, triiodothyronine, urea, uric acid, vitamin B12, zinc. Urine: albumine, creatinine, desoxypyridinoline, teststrip: bilirubin, blood (erythrocytes), glucose, ketones, leukocytes, nitrite, pH value, protein, specific weight, urobilinogen Dried blood cards: arsenic, brain derived neurotropic-factor, cadmium, chromium, fatty acids (C12:0, C14:0, C15:0, C16:0, C16:1n7, C17:0, C18:0, C18:1,t6-11, C18:1,c9, C18:1,c11, C18:2,n-6, C20:0, C18:3,n-6, C18:3,n-3, C20:1,n-9, C20:2,n-6, C22:0/C20:3,n-6, C20:4,n-6, C20:5,n-3, C24:0, C22:5,n-3, C22:6,n-3, unknown), HbA1c, hsCRP, lead, mercury, nickel, total-cholesterol
Genomics	Genome-wide single nucleotide polymorphism genotyping using the “Global Screening Array” (Illumina, Inc.); genome-wide DNA methylation profiling using the “Infinium MethylationEPIC” array (Illumina, Inc.)
Psychosocial questionnaire	Well-being, positive affect and negative affect, emotion regulation, stress, personality, control beliefs, domain-specific control, time perception, embitterment, loneliness, solitude, social activities, network structure, sexuality, risk behavior, etc.

Biobanking	Blood plasma & serum, urine, DNA extracted from EDTA-blood and buccal swaps
Cognitive tests	*Episodic memory* (Picture-Word-Task, Face-Profession-Task, Object Location Task, Scene-Encoding, Verbal learning and memory test), *Working memory* (Letter Updating, Spatial Updating, Number-N-Back), *Executive functioning / processing speed* (Multi-Source-Interference Task, Digit Symbol Substitutions Test[2]), *Fluid intelligence* (Letter series, Number series, Practical Problems), *Subjective Health Horizon Questionnaire* (SHH-Q)
Immunological assessment	Cryopreservation of whole blood (SmartTube system) or isolated PBMCs, and serum samples. Direct ex vivo staining of recent thymic emigrants (RTE, CD31+ CD45RA+ CD4+ T cells), TEMRA (CD45RA+ CD8+ T cells), Tregs (CD25bright CD127- CD4+ T cells), cytotoxic CD4+ Tcells, amongst others using four different panels: 1) ImmunoCount Panel (CD45, CD3, CD56, CD19, CD16, CD14, CD123, CD1c); 2) RTE panel (CD3, CD4, CD8, CD45RA, CCR7, CD31, CD95, CD11a); 3) TREG panel (CD3, CD4, CD8, CD25, CD127); 4) Effector T cell panel (CD3, CD4, CD8, CD45RA, CCR7, SLAM-F7, IL-6R, CD57, PD-1). Panels were measured on MacsQuant 10 (Miltenyi), MacsQuant 16 (Miltenyi) or LSR II (BD)

[1]only available for older group; [2]assessed at study visit 1 and 3, [3]blood samples were drawn after a fasting period of at least 8 hours (if not otherwise indicated), [4]post-load (75g glucose, 2h), not assessed in participants with known diabetes

Figure Legend:

Figure 1: Flow chart explaining the final BASE-II sample with follow-up assessments completed in GendAge

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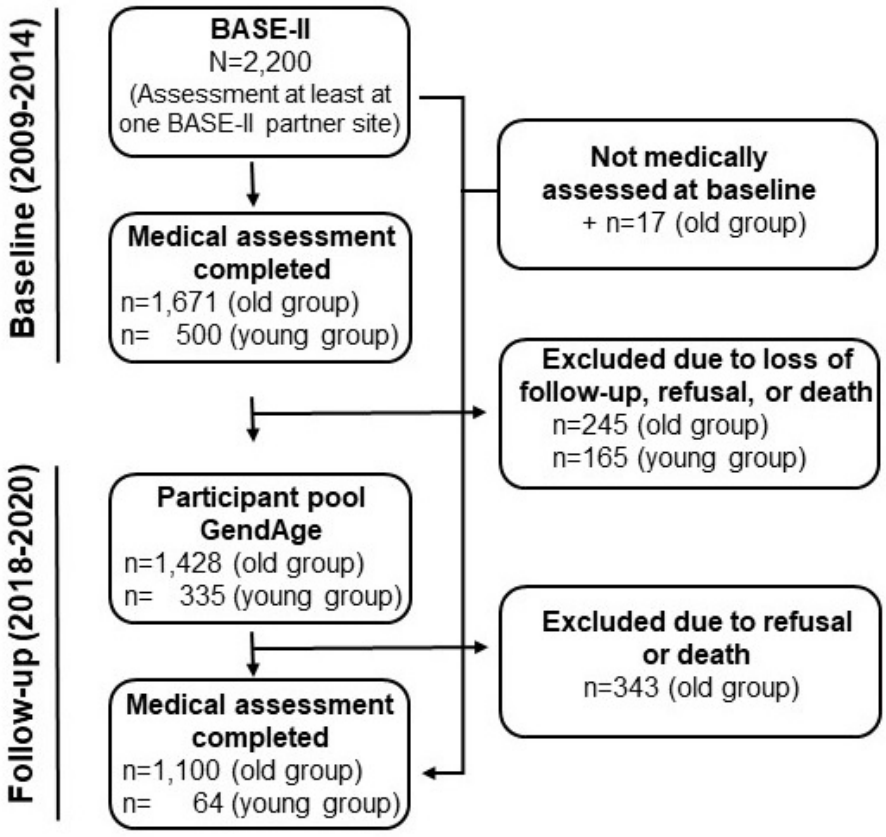

Figure 1: Flow chart explaining the final BASE-II sample with follow-up assessments completed in GendAge

153x144mm (96 x 96 DPI)

BMJ Open

Cohort Profile: Follow-up of a Berlin Aging Study II (BASE-II) subsample as part of the GendAge study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-045576.R1
Article Type:	Cohort profile
Date Submitted by the Author:	08-Apr-2021
Complete List of Authors:	Demuth, Ilja; Charité Universitätsmedizin Berlin, Banszerus, Verena; Charité Universitätsmedizin Berlin Drewelies, Johanna; Humboldt University of Berlin Düzel, Sandra; Max-Planck-Institute for Human Development Seeland, Ute; Charité Universitätsmedizin Berlin Spira, Dominik; Charité Universitätsmedizin Berlin Tse, Esther; Charité Universitätsmedizin Berlin Braun, Julian; Charité Universitätsmedizin Berlin Bertram, Lars ; University of Lubeck, Institutes of Neurogenetics & Integrative and Experimental Genomics Thiel, Andreas; Charite Universitatsmedizin Berlin Lindenberger, Ulman; Max-Planck-Institute for Human Development Regitz-Zagrosek, Vera; Charite Universitatsmedizin Berlin Gerstorf, Denis; Humboldt University of Berlin
Primary Subject Heading:	Public health
Secondary Subject Heading:	Diabetes and endocrinology, Geriatric medicine, Mental health, Public health
Keywords:	GENERAL MEDICINE (see Internal Medicine), GERIATRIC MEDICINE, PUBLIC HEALTH, VASCULAR MEDICINE

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Cohort Profile: Follow-up of a Berlin Aging Study II (BASE-II) subsample as part of the GendAge study

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Keywords: GendAge, Berlin Aging Study II, BASE-II

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Abstract

Purpose: The study "Sex- and gender-sensitive prevention of cardiovascular and metabolic disease in older adults in Germany", the GendAge study, focusses on major risk factors for cardiovascular and metabolic diseases and on the development of major outcomes from intermediate phenotypes in the context of sex and gender differences. It is based on a follow-up examination of a subsample (older group) of the Berlin Aging Study II (BASE-II).

Participants: The GendAge study assessments took place between 22 June 2018 and 10 March 2020. A total of 1,100 participants (older BASE-II subsample) with baseline data assessed at least by one of the BASE-II partner sites were investigated in the follow-up. These participants had a mean age of 75.6 years (SD ± 3.8), with a mean follow-up at 7.4 years (SD ± 1.5).

Findings to date:

Data from different domains such as internal medicine, geriatrics, immunology, and psychology were collected, with a focus on cardio-metabolic diseases and in the context of sex and gender differences. Diabetes mellitus type 2 was reported by 15.6% and 8.8% of men and women, respectively. In contrast, this disease was diagnosed in 20.7% of men and 13.3% of women, indicating that a substantial proportion of almost 30% was unaware of the disease. Echocardiography revealed that left ventricular ejection fraction was higher in women than in men, in agreement with previous reports.

Future plans: A gender questionnaire assessing sociocultural aspects implemented as part of the follow-up described here will allow to calculate a gender score and its evaluation based on the newly collected data. At the same time, the other BASE-II research foci established over the past 10 years will be continued and strengthened by the transition of BASE-II into a longitudinal study with follow-up data on the older subsample.

Registration: German Clinical Trials Register (Study-ID: DRKS00016157).

Strengths and limitations of this study

- The GendAge study focusses on major risk factors for cardiovascular and metabolic diseases and on the development of major outcomes from intermediate phenotypes in the context of sex and gender differences
- The BASE-II follow-up as part of the GendAge study assessments covered most of the medical, psycho-social and cognitive domains and variables assessed at baseline
- Comprehensive and longitudinal study data offer the potential to answer a number of questions that are of crucial relevance for the health of old women and men.
- The possibility of a selection bias in the follow-up study population is a limitation, which we have made various efforts to counteract
- We are able to systematically quantify the sampling bias and even account for it when it comes to the question of generalizability of study results to a population as a whole

Introduction

The original BASE-II cohort

The Berlin Aging Study II (BASE-II) was launched as a multidisciplinary study aimed at better understanding the multitude of different ways in which age and aging evolve and identifying underlying mechanisms and contributing factors. Baseline recruitment of 2,200 adult volunteers from the Berlin metropolitan area and baseline assessments were completed in 2014 [1]. The ascertainment protocol included the collection of data from different domains for each of the 2,200 participants (about 75% aged 60 years and above, the *older group* of BASE-II participants), namely geriatrics and internal medicine, immunology, genetics, psychology, sociology, and economics [1,2].

BASE-II baseline data were used in a multitude of analysis projects focusing on key questions revolving around age and aging. Research topics of the ongoing study include, but are not limited to, cognitive aging [3-5], cardiovascular and metabolic health [6-8], sarcopenia and frailty [9,10], psychosocial factors of aging [11,12], genetic risk factors of aging and disease [13-15], the impact of characteristics of the neighborhood people are living in [16], as well as indicators of biological age [17,18] and immune biomarkers [19]. For an overview of the BASE-II research foci and publications, refer to [20] and the BASE-II website (https://www.base2.mpg.de/en/project-information/publications).

Contact procedure – Follow-up assessments

Of the original BASE-II sample consisting of 2,200 participants 1,671 aged 60 years and above (=older group) were assessed medically at baseline between 2009 and 2014. The follow-up assessments within the GendAge study took place between 22 June 2018 and 10 March 2020 at the Charité Universitaetsmedizin Berlin. During the recruitment of the follow-up cohort, we approached all BASE-II participants of the remaining pool of 1,428 subjects out of the originally 1,671 subjects who completed the baseline medical assessments at an age of 60 years and

older (older BASE-II group, see Figure 1). Potential follow-up participants were contacted via telephone and an invitation letter that contained a comprehensive participant's information sheet. Letters of consent were sent at least five days before the scheduled first of two assessment days to all subjects who agreed to participate. As a result of a 4-week pilot phase, we reduced the maximum number of participants examined on each of the first two study days from 6 to 4, with an interval of usually 7 days between study visit one and two. Largely because of this early adjustment, follow-up examinations lasted 21 months instead of the 15 months originally planned. Moreover, another wave of cognitive assessments carried out by the Max Planck Institute for Human Development (MPIB) has been tightly linked to the GendAge assessment of BASE-II participants. The cognitive session (= third study visit) followed about seven days after the second medical examination.

What is the reason for the new data collection?

The study "Sex- and gender-sensitive prevention of cardiovascular and metabolic disease in older adults in Germany", the GendAge study, focusses on major risk factors for cardiovascular and metabolic diseases and on the development of major outcomes from intermediate phenotypes in the context of biological sex and gender differences. Major outcomes include but are not limited to myocardial infarction (MI), heart failure (HF) and diabetes mellitus type 2 (T2D), as well as mortality and quality of life. Gender was quantitated in two ways: by a retrospective approach, based on available data at study entry (2009-2014) and already published (GenderScore-I, GS-I [21]) as well as by a comprehensive gender questionnaire covering a range of socio-cultural gender characteristics as a central instrument. (GenderScore-II, GS-II). This questionnaire contains an adapted version of the gender questionnaire developed by Pelletier and colleagues covering most of the four gender aspects described by the Women Health Research Network of the Canadian Institute of Health Research (gender roles, gender identity, gender relations, and institutionalized gender) [22,23].. The variables finally constituting the GS-I were chronic stress, marital status, risk-taking

behaviour, personality attributes: agreeableness, neuroticism, extraversion, loneliness, conscientiousness, and level of education [21].

What will be the new areas of research?

There is new knowledge showing that sex differences play a role in all major diseases, their prevention and treatment [24]. Other studies showed that gender as the sociocultural dimension of being a woman or a man affects disease and treatment outcomes and also well-being [22,25]. The new areas of research cover the systemic inclusion of sex-specific analysis and the inclusion of gender. Aging interacts with sex and gender differences in health, but it is not clear, which mechanisms are most important.

GendAge aims to better understand, which mechanisms affect cardio-metabolic morbidity, mortality, and quality of life among older adults in a sex- and gender-sensitive manner.

While on different occasions follow-up data were ascertained for questionnaire and cognitive data [5,26-30], as being part of the GendAge study this cohort profile update describes the first comprehensive follow-up assessments in a BASE-II subsample (older group) that also includes a re-assessment of central variables in the areas of internal medicine and geriatrics.

Cohort description

As presented in the flow chart (Figure 1), following the contact procedure until the participant pool was exhausted resulted in a total of 1,100 participants of the older BASE-II group investigated in the follow-up. These participants had a mean age of 75.6 years (SD ± 3.8, range 64.9 - 94.1 years), with up to 10.4 years of follow-up (mean follow-up at 7.4 years, SD ± 1.5). At follow-up, almost all of the older participants were retired (97.3%) as compared with 86% at the time of baseline assessment. At baseline, BASE-II participants were characterized by higher education and better self-reported health status than the general population of Berlin and Germany [1]. At follow-up, this selection seems to have increased, with 68.8% of the participants reported to have a high school degree (51% at baseline) and about 61% rated their health as *very good* or *good* (40% at baseline). The rate of divorce had been above average at baseline with 29% and had dropped to 21.7% at follow-up, which is still significantly above the German and Berlin average (i.e. 12.0% and 17.4%, respectively)[31], while the proportion of widowed participants increased from 5% at baseline to 10.5% in the follow-up dataset of older BASE-II participants. As shown in Table 1, differences between men and women are evident with respect to the sociodemographic status and psychosocial functioning in the follow-up cohort: Men reported significantly higher school degrees and higher satisfaction with life in general than women. Interestingly, self-rated health did not differ between men and women, which matches to the overall morbidity estimated by an adapted version of the Charlson morbidity index [17,32], which also did not differ between men and woman ($p=0.98$, Table 1). This morbidity index, however, increased between baseline and follow-up ($p<0.001$, Wilcoxon signed-rank test and data not shown). Differences between men and women exist in the follow-up dataset with respect to the prevalence of some, but not all cardiovascular risk factors and diseases (Table 1). Men for example had a higher BMI and a higher proportion of men reported to have T2D and myocardial infarction than women. No significant differences between men and women were evident in the reporting of hypertension, peripheral artery disease, and stroke. With the aim of investigating human ageing processes

in BASE-II under consideration of different disciplines and longitudinally, the baseline investigation aimed at the most comprehensive data collection possible. At follow-up, most of these data in the field of geriatrics, internal medicine and psychology were again part of the study protocol (for a select overview, see Table 2).

Findings to date

With a focus on cardio-metabolic diseases in GendAge, we extended the broad range of data assessed in this area at baseline by echocardiography. Data on right and left ventricular and atrial morphology and systolic and diastolic function and vascular stiffness were obtained. Left ventricular ejection fraction (LVEF) was higher in women than in men, in agreement with previous reports [33 34]. Furthermore, increased LV mass and volumes in men before and after indexing to BMI were confirmed, underscoring major sex differences in cardiovascular pathophysiology [35].

With the aim of achieving a particularly high-quality standard in the assessment of participant's medical history at baseline and follow-up, including past and current diseases, the information given by the participants was recorded from study physicians as part of a structured one-to-one interview, allowing to consider its plausibility. This, however, does not cover the gap between reported (anamnestic) diseases and the diseases diagnosed in the course of the study. This is exemplified by T2D, which was reported by 15.6% and 8.8% of men and women, respectively. In contrast, this disease was diagnosed in 20.7% of men and 13.3% of women based on the ADA guidelines 2019 [36], indicating that a substantial proportion of almost 30% was unaware of the disease (Table1).

As part of our endeavors, we have developed a retrospective gender score taking BASE-II baseline data reflecting sociocultural aspects (e.g., level of education, marital status, and chronic stress) into account. This retrospective gender score (GS-I) was associated with a number of clinical and psychosocial variables and performed better in predicting differences in a subset of variables (e.g. depression and life satisfaction) compared to biological sex[21]. In addition, we have implemented a comprehensive gender questionnaire as part of the follow-up assessments described here, to calculate a prospective gender score as proposed by Pelletier and colleagues [22].

Peripheral blood mononuclear cells were prepared from 903 participants at follow-up, of which 845 were fully analyzable (58 were dropouts) and frequencies as well as absolute counts of

recent thymic emigrants (RTEs), T_{EMRA} effector T cell subsets (T_{EMRA}) and cytotoxic $CD4^+$ T cells were directly assessed. While RTEs are known to decrease with ageing [37], alterations in T_{EMRA} and specialised cytotoxic $CD4^+$ T cell compartments can be indicative of age-related perturbations of systemic T cell immunity [38]. The immunological screening has so far revealed significantly higher frequencies of RTEs in women as compared to men, indicating a higher thymic T cell production even at the advanced ages of the GendAge participants. In men, more $CD45RA^+$ re-expressing TEMRAs were detected than in women (Table 1). These cells are associated with chronic viral infections (e.g. CMV) and can serve as a signature of immune-senescence [39]. We found no significant difference in the frequencies of cytotoxic $CD4^+$ T cells. Together, these preliminary findings confirm the better immune status of aged women as compared to men. A detailed analysis of the datasets will identify additional correlates of sex and gender, aging, and the immune system.

The gender questionnaire implemented as part of the follow-up assessments described here will allow to calculate a gender score and its evaluation based on the newly collected clinical and psychosocial follow-up data. At the same time, the other BASE-II research foci established over the past 10 years will be continued and strengthened with the transition of BASE-II into a longitudinal study with follow-up data on the older subsample.

Other measurements

Similar to baseline, we determined numerous routine laboratory parameters from blood and urine (Table 2), and also stored blood plasma/serum and urine samples for future analyses. Genomic DNA was already extracted from EDTA-blood and buccal swab samples from GendAge participants, which will be used e.g. for the profiling of genome-wide DNA methylation signatures and new genome-wide single nucleotide polymorphism genotyping experiments (Table 2). In-between the two assessment days at the Charité, participants were asked to fill out a comprehensive psychosocial take-home questionnaire and return this at their second Charité visit.

At baseline, the BASE-II included a group of 600 younger subjects aged 20-35 years serving as a reference population [1], of which 500 completed baseline medical assessments. Between 7 February 2020 and 13 March 2020, we performed follow-up assessments in a total of 64 participants of this younger group until these assessments were suspended because of the SARS-Cov2 pandemic. These younger participants had a mean age of 36.8 years (SD ± 3.5, range 29.3 - 44.1 years), with up to 10.7 years of follow-up (minimum 6.1 years, mean follow-up at 8.2 years, SD ± 1.6). Follow-up for these younger BASE-II participants essentially followed the protocol used for the 1,100 older BASE-II participants. Because this younger group is not primarily part of the analyses planned in GendAge, further details about this group will be described elsewhere.

The cognitive session carried out by the Max Planck Institute for Human Development (MPIB) lasted about 4.5 to 5 hours (third study visit). Subjects were tested in groups of 4–6 individuals. The cognitive battery included 17 measures of learning and memory performance, attention/processing speed, working memory, executive functioning, and perceptual speed (see Table 2). Within the week between study visit 2 (Charité) and 3 (MPIB) accelerometers (ActiGraph wGT3X-BT) have been used to track participants' physical activity and sleep in a subset of our participants (N=750).

After the cognitive session, participants were invited to take part in a one-to-one interview on a different day. This additional individual assessment took up to 60 minutes and serves as a cohort comparison between the BASE and BASE-II study populations. This additional data collection will also contribute to the BASE-II cognitive waves, allowing us to further investigate individual differences in aging trajectories (for an overview, refer to[20]).

Furthermore, and as part of a collaboration with the Lifebrain study, a consortium of European studies funded by the EU Horizon 2020 Framework Programme[40], we collected blood samples using dried blood cards, in order to determine laboratory parameters with identical methods used for all Lifebrain participating sites. Lifebrain aims at identifying determinants of healthy lifespan development by integrating and harmonizing data and results from 11 large and

predominantly longitudinal European samples from 7 countries. This has yielded a database of fine-grained measures focusing on brain and cognition from more than 7,000 individual participants.

The GendAge study was approved by the Ethics Committee of the Charité–Universitätsmedizin Berlin (approval number EA2/144/16) and all participants gave written informed consent. GendAge is registered in the German Clinical Trials Register (Study-ID: DRKS00016157). The cognitive battery was approved by the Ethics Committee of the Max-Planck-Institute and the genomics experiments were approved by the Ethics Committees of the Charité (approval number EA2/144/16) and the University of Lübeck (approval numbers AZ19-390A and 19-391A).

Strengths and limitations

The BASE-II follow-up assessments covered most of the medical, psycho-social and cognitive domains and variables assessed at baseline, and thereby taking the BASE-II characteristic of an exceptionally broad and in-depth data collection to a next, longitudinal level. In addition, and in the context of the GendAge focus on cardio-metabolic disease, we extended the assessments in this area e.g. by including high-quality echocardiography resulting in a unique data collection. This strength with respect to comprehensive and longitudinal data offers the potential to answer a number of questions that are of crucial relevance for the health of old women and men. Thus, GendAge will make important contributions for improvements in understanding the health and well-being of older adults in both genders. BASE-II was initiated as a multidisciplinary study with expertise in a broad range of fields relevant for aging research (e.g. internal medicine and geriatrics, biology, psychology, genetics, immunology, socio-economics, and now in GendAge further extended by socio-cultural aspects of gender). The past ten years of BASE-II research have shown that multidisciplinary collaboration is not only a statement of intent, but a fruit-bearing working posture and a clear strength of BASE-II.

Sampling bias is a challenge which cohort studies have to deal with, and this is especially an issue in the follow-up of older study populations such as the older group of BASE-II participants. To address this, we have made a considerable effort (e.g. offering a taxi service for participants not able to travel independently) to include as many participants in the follow-up as possible. Additionally, and similar to baseline, we are able to systematically quantify the sampling bias and even account for it when it comes to the question of generalizability of study results to a population as a whole (e.g., Berlin or Germany), due to the evaluation of selectivity and representativeness via the German Socio-Economic Panel Study (SOEP) [1]. Despite these possibilities we cannot rule out the possibility of a selection bias completely, which certainly is a weakness of this study, a weakness that applies to all cohort studies relying on voluntary participants who have been non-randomly recruited. With our direct comparability to the

national representative SOEP study, we are in a position though to quantify the amount of selectivity and, if need, take measures to correct and adjust our results.

Collaboration

More details on GendAge can be found at https://gendage.charite.de/en/ and information on the BASE-II as a whole is available at https://www.base2.mpg.de/en. BASE-II has a tradition of sharing data and biobank samples in joint collaborative projects which will be continued with respect to BASE-II data assessed in GendAge. Interested groups are invited to contact the study coordinating PI Ilja Demuth at ilja.demuth@charite.de for the data-sharing application form. Each application will be reviewed by the GendAge PIs (currently ID, VRZ and DG) and the decision communicated to the applicants usually within 4 weeks of submission.

Participant and public involvement

Participants and public were not involved in the design or conduct of this study.

Funding statement

The GendAge study research project (Co-PIs are Ilja Demuth, Vera Regitz-Zagrosek, and Denis Gerstorf) is supported by the German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung, BMBF) grant numbers 01GL1716A (ID and VRZ) and 01GL1716B (DG). Genomics assessments are funded by the Cure Alzheimer's Fund (as part of the "CIRCUITS-AD" consortium project) and the European Research Council's "Horizon2020" funding scheme (as part of the "Lifebrain" consortium project; both to LB). Additional contributions (e.g., equipment, logistics, personnel) are made from each of the participating sites.

Contributorship statement

Conceived and designed the study: ID, VRZ, SD, UL and DG. Collected study specific data: I.D., VLB, JD, SD, US, DS, ET, JB, LB and AT. Analysed the data: ID, ET and JB. Wrote the manuscript: ID. All authors revised and approved the manuscript.

Acknowledgements

We are deeply indebted to all individuals of the BASE-II cohort who have agreed to participate in the follow-up assessments. We would further like to thank all staff members and students involved in the medical examinations of participants and documentation, especially Nora Berger, Janina Dombrowski, Mergim Domuzeti, Elisa Dreißig, Ilona Enarovic, Anthony Ganswindt, Thomas Grenkowitz, Anna Hunold, Ilias Katsianas, Yoo-Ri Kim, Jörn Kiselev, Paula Krull, Christine Kytmannow, Elisa Lemke, Julia Mätzkow, Charlotte Mentzel,

Nadja Mielke, Narantuya Mishig, Angela Motz, Eduard Nitschke, Aabi Okute, Danai Pantelakis, Sophie Poser, Johanne Spieker and Taleka Vollmar (all Charité Universitaetsmedizin Berlin, Biology of Aging group); and Luisa Lüth, Mariebelle Kaus, Isabel Ganter, Marlene Rosendahl, Jasmin Boneberger, Antonia Sprenger, Hania El-Kersh (all Humboldt University, Department of Psychology), and Kirsten Becker for the excellent daily organization of the running study within and between the research units, the Telefonstudio for their daily contact with the participants, Martin Becker for the continuous quality checks of our sample and Berndt Wischnewski for updating the database and cognitive battery (all Max Planck Institute for Human Development).

We kindly acknowledge the excellent cooperation with the Central Biomaterial Bank, the joint core facility of the Charité-Universitätsmedizin Berlin and the Berlin Institute for Health (BIH). Furthermore, we appreciate the great support by the BIH-REDCap team and especially from Andreas Hetey. We would like to acknowledge the assistance of the Charité|BIH Cytometry Core.

Conflict of interest: None declared.

Data availability statement

Data are available upon reasonable request. The GendAge study principal investigators welcome new collaborations with other investigators. Interested investigators are invited to contact the study coordinating PI Ilja Demuth at ilja.demuth@charite.de to obtain additional information about the GendAge study and the data-sharing application form.

Tables

Table 1: Selection of BASE-II follow-up characteristics as assessed of the GendAge study

	Total number of observations	Women[1] (N=573, 52.1%)	Men[1] (N=527, 47.9%)	*p-value*[2]
Age (years)	1,100	75.7 (± 3.5)	75.5 (± 4.0)	0.276
Highest school degree Elementary school Intermediate school High school	1,095	35 (6.1%) 183 (32.0%) 354 (61.9%)	18 (3.4%) 104 (19.9%) 401 (76.7%)	<0.001
Family status Married Not married, in partnership Single Divorced Widowed Other	1,098	218 (38.0%) 12 (2.1%) 60 (10.5%) 187 (32.6) 89 (15.5%) 7 (1.2%)	386 (73.5%) 19 (3.6%) 33 (6.3%) 51 (9,7%) 26 (5.0%) 10 (1.9)	<0.001
Employment status Retired	1,055	540 (97.6)	486 (96.8)	0.689
Self-rated health Very good Good Fair Poor or very poor	1,096	56 (9.8%) 284 (49.7%) 166 (29.0%) 66 (11.5%)	65 (12.4%) 262 (50.0%) 143 (27.3%) 54 (10.3%)	0.499
Satisfaction with life in general	1,097	7.9 (±1.6)	8.1 (±1.4)	<0.05
Digit Symbol Substitution Test[3]	1,095	41.37(±8.48)	39.21(±9.67)	<0.001
Verbal learning test	925	41.6 (±12.3)	44.0 (±12.8)	<0.01
Depression (ever diagnosed)	1,095	122 (21.3%)	63 (12.0%)	<0.001
BMI	1,098	26.6 (±4.7)	27.4 (±3.7)	<0.01
Physical inactive[4]	1,096	67 (11.7%)	65 (12.4%)	0.781
Diabetes mellitus type II (self-reported)	1,097	49 (8.6%)	82 (15.6%)	<0.001
Diabetes mellitus type II (diagnosed/ ADA guidelines 2019)	1,097	76 (13.3%)	109 (20.7%)	<0.01
Metabolic Syndrome (diagnosed, AHA/IDF/NHLBI criteria 2009)	1,074	252 (45.5%)	327 (62.9%)	<0.001
Hypertension	1,097	296 (51.7%)	311 (59.2%)	<0.05
Myocardial infarction	1,097	11 (1.9%)	24 (4.6%)	<0.05
Stroke	1,096	13 (2.3%)	20 (3.8%)	0.158
Peripheral artery disease	1,094	8 (1.4%)	15 (2.9%)	0.138

Morbidity index	955	1.0 (IQR 2.0)	1.0 (IQR 2.0)	0.594
Pulse wave velocity (m/s)	932	11.21 (±0.92)	11.04 (±0.91)	<0.01
Left ventricular ejection fraction (%)	773	64.12 (±6.24)	62.92 (±5.76)	<0.01
Left ventricular mass (g)	691	135.24 (±31.87)	179.76 (±38.96)	<0.001
Left ventricular mass index (g)[5]	690	78.55 (±16.83)	91.22 (±17.96)	<0.001
Left ventricular end-diastolic volume (ml)[5]	773	54.10 (±12.24)	63.67 (±13.58)	<0.001
Frailty (Fried) Not frail Pre-frail Frail	1,087	 260 (45.4%) 280 (48.9%) 28 (4.9%)	 251 (47.6%) 248 (47.1%) 20 (3,8%)	 0.542
Maximal hand grip strength (kg)	1,098	20.5 (±4.4)	35.1 (±6.8)	<0.001
Recent thymic emigrants (naïve CD4⁺ T cells)	395[6]	64.69 (± 16.34)	51.03 (± 13.69)	<0.001
T_{EMRA} (effector memory T cells re-expressing CD45RA)	395[6]	32.82 (± 19.96)	34.94 (± 21.29)	0.309
Cytotoxic SLAMF7+ CD4⁺ T cells	181[7]	6.02 (± 5.98)	6.05 (± 6.60)	0.974

[1]Data are presented as N (%), mean ±standard deviation or median (interquartile range, IQR). [2]Differences between women and men were assessed using the parametric t test, the nonparametric Mann-Whitney U test or the $\chi 2$ where appropriate. [3]Assessed at study visit 1. [4]Assessed with the question “Are you seldom or never physically active?”. [5]Adjusted for body surface area. [6]845 expected to be available after completion of the analyses. [7]629 expected to be available after completion of the analyses.

Table 2: BASE-II follow-up assessments during the two GendAge study visits and the cognitive sessions (third study visit)

Type of assessment/ domain	Example assessments/tests
Physical examination and medical history	Medical history structured by organ systems, medication, body weight, height, lifestyle (including smoking status, alcohol consumption, physical activity)
Physical status and functional tests	Tinetti Mobility Test, Timed up & Go Test, Barthel Index (ADL), Lawton Instrumental Activities of Daily Living Scale (IADL), hand grip strength, anthropometric parameters, pulse wave velocity/ arterial stiffness (Mobil-o-Graph), echocardiography, electrocardiography (ECG), spirometry, motion monitoring (Actigraph), dual-energy X-ray absorptiometry (DXA),
Psychological screening tests	Mini Mental State Examination (MMSE), Digit Symbol Substitution Test (DSST) [1], Center for Epidemiologic Studies Depression Scale (CESD)
Questionnaires	EPIC (food-frequency questionnaire), Gender Questionnaire, Pittsburgh Sleep Quality Index, Rapid Assessment of Physical Activity, SARC-F , SF-36
Laboratory values[2]	Blood, serum or plasma: 25-hydroxyvitamin D, apolipoprotein A1, apolipoprotein B, basophiles, calcium, cortisol, creatinine, creatinine kinase, C-reactive protein, cystatin C, dehydroepiandrosterone, eosinophils, erythrozytes, ferritin, folic acid, gamma-glutamyltransferase, glucose 1, glucose 2[3], glutamate, oxalacetate transaminase, glutamate-pyruvate transaminase, HbA1c, HDL-cholesterol, hematocrit, hemoglobin, homocysteine, international normalized ratio, iron, LDL-

	cholesterol, leukocytes, lipoprotein (a), lymphocytes, magnesium, MCH, MCHC, MCV, monocytes, neutrophils, oestradiol, osteocalcin, partial thromboplastin time, RDW, sex hormone-binding globulin, testosterone, thrombocytes, thyroid-stimulating hormone, thyroxine, total-cholesterol, triglycerides, triiodothyronine, urea, uric acid, vitamin B12, zinc. Urine: albumine, creatinine, desoxypyridinoline, teststrip: bilirubin, blood (erythrocytes), glucose, ketones, leukocytes, nitrite, pH value, protein, specific weight, urobilinogen Dried blood cards: arsenic, brain derived neurotropic-factor, cadmium, chromium, fatty acids (C12:0, C14:0, C15:0, C16:0, C16:1n7, C17:0, C18:0, C18:1,t6-11, C18:1,c9, C18:1,c11, C18:2,n-6, C20:0, C18:3,n-6, C18:3,n-3, C20:1,n-9, C20:2,n-6, C22:0/C20:3,n-6, C20:4,n-6, C20:5,n-3, C24:0, C22:5,n-3, C22:6,n-3, unknown), HbA1c, hsCRP, lead, mercury, nickel, total-cholesterol
Genomics	Genome-wide single nucleotide polymorphism genotyping using the “Global Screening Array” (Illumina, Inc.); genome-wide DNA methylation profiling using the “Infinium MethylationEPIC” array (Illumina, Inc.)
Psychosocial questionnaire	Well-being, positive affect and negative affect, emotion regulation, stress, personality, control beliefs, domain-specific control, time perception, embitterment, loneliness, solitude, social activities, network structure, sexuality, risk behavior, etc.

Biobanking	Blood plasma & serum, urine, DNA extracted from EDTA-blood and buccal swaps
Cognitive tests (third study visit)	*Episodic memory* (Picture-Word-Task, Face-Profession-Task, Object Location Task, Scene-Encoding, Verbal learning and memory test), *Working memory* (Letter Updating, Spatial Updating, Number-N-Back), *Executive functioning / processing speed* (Multi-Source-Interference Task, Digit Symbol Substitutions Test[1]), *Fluid intelligence* (Letter series, Number series, Practical Problems), *Subjective Health Horizon Questionnaire* (SHH-Q)
Immunological assessment	Cryopreservation of whole blood (SmartTube system) or isolated PBMCs, and serum samples. Direct ex vivo staining of recent thymic emigrants (RTE, CD31+ CD45RA+ CD4+ T cells), TEMRA (CD45RA+ CD8+ T cells), Tregs (CD25bright CD127- CD4+ T cells), cytotoxic CD4+ Tcells, amongst others using four different panels: 1) ImmunoCount Panel (CD45, CD3, CD56, CD19, CD16, CD14, CD123, CD1c); 2) RTE panel (CD3, CD4, CD8, CD45RA, CCR7, CD31, CD95, CD11a); 3) TREG panel (CD3, CD4, CD8, CD25, CD127); 4) Effector T cell panel (CD3, CD4, CD8, CD45RA, CCR7, SLAM-F7, IL-6R, CD57, PD-1). Panels were measured on MacsQuant 10 (Miltenyi), MacsQuant 16 (Miltenyi) or LSR II (BD)

[1]assessed at study visit 1 and 3, [2]blood samples were drawn after a fasting period of at least 8 hours (if not otherwise indicated), [3]post-load (75g glucose, 2h), not assessed in participants with known diabetes

Figure Legend:

Figure 1: Flow chart explaining the final BASE-II sample with follow-up assessments completed in GendAge

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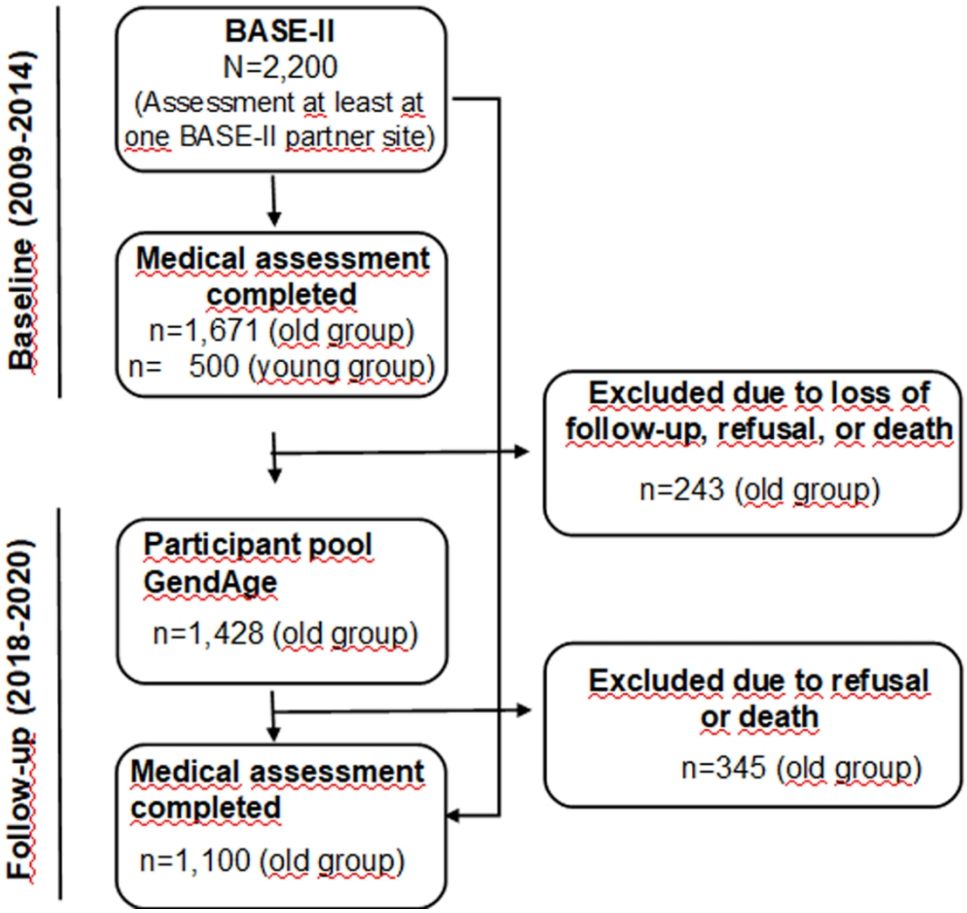

Figure 1: Flow chart explaining the final BASE-II sample with follow-up assessments completed in GendAge

99x90mm (300 x 300 DPI)

BMJ Open

Cohort Profile: Follow-up of a Berlin Aging Study II (BASE-II) subsample as part of the GendAge study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-045576.R2
Article Type:	Cohort profile
Date Submitted by the Author:	04-May-2021
Complete List of Authors:	Demuth, Ilja; Charité Universitätsmedizin Berlin, Banszerus, Verena; Charité Universitätsmedizin Berlin Drewelies, Johanna; Humboldt University of Berlin Düzel, Sandra; Max-Planck-Institute for Human Development Seeland, Ute; Charité Universitätsmedizin Berlin Spira, Dominik; Charité Universitätsmedizin Berlin Tse, Esther; Charité Universitätsmedizin Berlin Braun, Julian; Charité Universitätsmedizin Berlin Steinhagen-Thiessen, Elisabeth; Charité Universitätsmedizin Berlin Bertram, Lars ; University of Lubeck, Institutes of Neurogenetics & Integrative and Experimental Genomics Thiel, Andreas; Charite Universitatsmedizin Berlin Lindenberger, Ulman; Max-Planck-Institute for Human Development Regitz-Zagrosek, Vera; Charite Universitatsmedizin Berlin Gerstorf, Denis; Humboldt University of Berlin
Primary Subject Heading:	Public health
Secondary Subject Heading:	Diabetes and endocrinology, Geriatric medicine, Mental health, Public health
Keywords:	GENERAL MEDICINE (see Internal Medicine), GERIATRIC MEDICINE, PUBLIC HEALTH, VASCULAR MEDICINE

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Cohort Profile: Follow-up of a Berlin Aging Study II (BASE-II) subsample as part of the GendAge study

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Keywords: GendAge, Berlin Aging Study II, BASE-II

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Abstract

Purpose: The study "Sex- and gender-sensitive prevention of cardiovascular and metabolic disease in older adults in Germany", the GendAge study, focusses on major risk factors for cardiovascular and metabolic diseases and on the development of major outcomes from intermediate phenotypes in the context of sex and gender differences. It is based on a follow-up examination of a subsample (older group) of the Berlin Aging Study II (BASE-II).

Participants: The GendAge study assessments took place between 22 June 2018 and 10 March 2020. A total of 1,100 participants (older BASE-II subsample, aged ≥65 years) with baseline data assessed at least by one of the BASE-II partner sites were investigated in the follow-up. These participants had a mean age of 75.6 years (SD ± 3.8), with a mean follow-up at 7.4 years (SD ± 1.5).

Findings to date:

Data from different domains such as internal medicine, geriatrics, immunology, and psychology were collected, with a focus on cardio-metabolic diseases and in the context of sex and gender differences. Diabetes mellitus type 2 was reported by 15.6% and 8.8% of men and women, respectively. In contrast, this disease was diagnosed in 20.7% of men and 13.3% of women, indicating that a substantial proportion of almost 30% was unaware of the disease. Echocardiography revealed that left ventricular ejection fraction was higher in women than in men, in agreement with previous reports.

Future plans: A gender questionnaire assessing sociocultural aspects implemented as part of the follow-up described here will allow to calculate a gender score and its evaluation based on the newly collected data. At the same time, the other BASE-II research foci established over the past 10 years will be continued and strengthened by the BASE-II transition into a longitudinal study with follow-up data on the older subsample.

Registration: German Clinical Trials Register (Study-ID: DRKS00016157).

Strengths and limitations of this study

- The GendAge study focusses on major risk factors for cardiovascular and metabolic diseases and on the development of major outcomes from intermediate phenotypes in the context of sex and gender differences
- The BASE-II follow-up as part of the GendAge study assessments covered most of the medical, psycho-social and cognitive domains and variables assessed at baseline
- Comprehensive and longitudinal study data offer the potential to answer a number of questions that are of crucial relevance for the health of old women and men.
- The possibility of a selection bias in the follow-up study population is a limitation, which we have made various efforts to counteract
- We are able to systematically quantify the sampling bias and even account for it when it comes to the question of generalizability of study results to a population as a whole

Introduction

The original BASE-II cohort

The Berlin Aging Study II (BASE-II) was launched as a multidisciplinary study aimed at better understanding the multitude of different ways in which age and aging evolve and identifying underlying mechanisms and contributing factors. Baseline recruitment of 2,200 adult volunteers from the Berlin metropolitan area and baseline assessments were completed in 2014 [1]. The ascertainment protocol included the collection of data from different domains for each of the 2,200 participants (about 75% aged 60 years and above, the *older group* of BASE-II participants), namely geriatrics and internal medicine, immunology, genetics, psychology, sociology, and economics [1,2].

BASE-II baseline data were used in a multitude of analysis projects focusing on key questions revolving around age and aging. Research topics of the ongoing study include, but are not limited to, cognitive aging [3-5], cardiovascular and metabolic health [6-8], sarcopenia and frailty [9,10], psychosocial factors of aging [11,12], genetic risk factors of aging and disease [13-15], the impact of characteristics of the neighborhood people are living in [16], as well as indicators of biological age [17,18] and immune biomarkers [19]. For an overview of the BASE-II research foci and publications, refer to [20] and the BASE-II website (https://www.base2.mpg.de/en/project-information/publications).

Contact procedure – Follow-up assessments

Of the original BASE-II sample consisting of 2,200 participants 1,671 aged 60 years and above (=older group) were assessed medically at baseline between 2009 and 2014. The follow-up assessments within the GendAge study took place between 22 June 2018 and 10 March 2020 at the Charité Universitaetsmedizin Berlin. During the recruitment of the follow-up cohort, we approached all BASE-II participants of the remaining pool of 1,428 subjects out of the originally 1,671 subjects who completed the baseline medical assessments at an age of 60 years and

older (older BASE-II group, see Figure 1). Between 7 February 2020 and 13 March 2020, we additionally performed follow-up assessments in a total of 64 participants of the younger BASE-II group aged 20-35 years at baseline until these assessments were suspended because of the SARS-Cov2 pandemic. Potential follow-up participants were contacted via telephone and an invitation letter that contained a comprehensive participant's information sheet. Letters of consent were sent at least five days before the scheduled first of two assessment days to all subjects who agreed to participate. As a result of a 4-week pilot phase, we reduced the maximum number of participants examined on each of the first two study days from 6 to 4, with an interval of usually 7 days between study visit one and two. Largely because of this early adjustment, follow-up examinations lasted 21 months instead of the 15 months originally planned. Moreover, another wave of cognitive assessments carried out by the Max Planck Institute for Human Development (MPIB) has been tightly linked to the GendAge assessment of BASE-II participants. The cognitive session (= third study visit) followed about seven days after the second medical examination.

What is the reason for the new data collection?

The study "Sex- and gender-sensitive prevention of cardiovascular and metabolic disease in older adults in Germany", the GendAge study, focusses on major risk factors for cardiovascular and metabolic diseases and on the development of major outcomes from intermediate phenotypes in the context of biological sex and gender differences. Major outcomes include but are not limited to myocardial infarction (MI), heart failure (HF) and diabetes mellitus type 2 (T2D), as well as mortality and quality of life. Gender was quantitated in two ways: by a retrospective approach, based on available data at study entry (2009-2014) and already published (GenderScore-I, GS-I [21]) as well as by a comprehensive gender questionnaire covering a range of socio-cultural gender characteristics as a central instrument. (GenderScore-II, GS-II). This questionnaire contains an adapted version of the gender questionnaire developed by Pelletier and colleagues covering most of the four gender aspects described by the Women Health Research Network of the Canadian Institute of Health

Research (gender roles, gender identity, gender relations, and institutionalized gender) [22,23].. The variables finally constituting the GS-I were chronic stress, marital status, risk-taking behaviour, personality attributes: agreeableness, neuroticism, extraversion, loneliness, conscientiousness, and level of education [21].

What will be the new areas of research?

There is new knowledge showing that sex differences play a role in all major diseases, their prevention and treatment [24]. Other studies showed that gender as the sociocultural dimension of being a woman or a man affects disease and treatment outcomes and also well-being [22,25]. The new areas of research cover the systemic inclusion of sex-specific analysis and the inclusion of gender. Aging interacts with sex and gender differences in health, but it is not clear, which mechanisms are most important.

GendAge aims to better understand, which mechanisms affect cardio-metabolic morbidity, mortality, and quality of life among older adults in a sex- and gender-sensitive manner.
While on different occasions follow-up data were ascertained for questionnaire and cognitive data [5,26-30], as being part of the GendAge study this cohort profile update describes the first comprehensive follow-up assessments in a BASE-II subsample (older group) that also includes a re-assessment of central variables in the areas of internal medicine and geriatrics.

Cohort description

As presented in the flow chart (Figure 1), following the contact procedure until the participant pool was exhausted resulted in a total of 1,100 participants of the older BASE-II group investigated in the follow-up. These participants had a mean age of 75.6 years (SD ± 3.8, range 64.9 - 94.1 years), with up to 10.4 years of follow-up (mean follow-up at 7.4 years, SD ± 1.5). At follow-up, almost all of the older participants were retired (97.3%) as compared with 86% at the time of baseline assessment. At baseline, BASE-II participants were characterized by higher education and better self-reported health status than the general population of Berlin and Germany [1]. At follow-up, this selection seems to have increased, with 68.8% of the participants reported to have a high school degree (51% at baseline) and about 61% rated their health as *very good* or *good* (40% at baseline). The rate of divorce had been above average at baseline with 29% and had dropped to 21.7% at follow-up, which is still significantly above the German and Berlin average (i.e. 12.0% and 17.4%, respectively)[31], while the proportion of widowed participants increased from 5% at baseline to 10.5% in the follow-up dataset of older BASE-II participants. As shown in Table 1, differences between men and women are evident with respect to the sociodemographic status and psychosocial functioning in the follow-up cohort: Men reported significantly higher school degrees and higher satisfaction with life in general than women. Interestingly, self-rated health did not differ between men and women, which matches to the overall morbidity estimated by an adapted version of the Charlson morbidity index [17,32], which also did not differ between men and woman ($p=0.98$, Table 1). This morbidity index, however, increased between baseline and follow-up ($p<0.001$, Wilcoxon signed-rank test and data not shown). Differences between men and women exist in the follow-up dataset with respect to the prevalence of some, but not all cardiovascular risk factors and diseases (Table 1). Men for example had a higher BMI and a higher proportion of men reported to have T2D and myocardial infarction than women. No significant differences between men and women were evident in the reporting of hypertension, peripheral artery disease, and stroke. With the aim of investigating human ageing processes

in BASE-II under consideration of different disciplines and longitudinally, the baseline investigation aimed at the most comprehensive data collection possible. At follow-up, most of these data in the field of geriatrics, internal medicine and psychology were again part of the study protocol (for a select overview, see Table 2).

Findings to date

With a focus on cardio-metabolic diseases in GendAge, we extended the broad range of data assessed in this area at baseline by echocardiography. Data on right and left ventricular and atrial morphology and systolic and diastolic function and vascular stiffness were obtained. Left ventricular ejection fraction (LVEF) was higher in women than in men, in agreement with previous reports [33 34]. Furthermore, increased LV mass and volumes in men before and after indexing to BMI were confirmed, underscoring major sex differences in cardiovascular pathophysiology [35].

With the aim of achieving a particularly high-quality standard in the assessment of participant's medical history at baseline and follow-up, including past and current diseases, the information given by the participants was recorded from study physicians as part of a structured one-to-one interview, allowing to consider its plausibility. This, however, does not cover the gap between reported (anamnestic) diseases and the diseases diagnosed in the course of the study. This is exemplified by T2D, which was reported by 15.6% and 8.8% of men and women, respectively. In contrast, this disease was diagnosed in 20.7% of men and 13.3% of women based on the ADA guidelines 2019 [36], indicating that a substantial proportion of almost 30% was unaware of the disease (Table1).

As part of our endeavors, we have developed a retrospective gender score taking BASE-II baseline data reflecting sociocultural aspects (e.g., level of education, marital status, and chronic stress) into account. This retrospective gender score (GS-I) was associated with a number of clinical and psychosocial variables and performed better in predicting differences in a subset of variables (e.g. depression and life satisfaction) compared to biological sex[21]. In addition, we have implemented a comprehensive gender questionnaire as part of the follow-up assessments described here, to calculate a prospective gender score as proposed by Pelletier and colleagues [22].

Peripheral blood mononuclear cells were prepared from 903 participants at follow-up, of which 845 were fully analyzable (58 were dropouts) and frequencies as well as absolute counts of

recent thymic emigrants (RTEs), T_{EMRA} effector T cell subsets (T_{EMRA}) and cytotoxic $CD4^+$ T cells were directly assessed. While RTEs are known to decrease with ageing [37], alterations in T_{EMRA} and specialised cytotoxic $CD4^+$ T cell compartments can be indicative of age-related perturbations of systemic T cell immunity [38]. The immunological screening has so far revealed significantly higher frequencies of RTEs in women as compared to men, indicating a higher thymic T cell production even at the advanced ages of the GendAge participants. In men, more $CD45RA^+$ re-expressing TEMRAs were detected than in women (Table 1). These cells are associated with chronic viral infections (e.g. CMV) and can serve as a signature of immune-senescence [39]. We found no significant difference in the frequencies of cytotoxic $CD4^+$ T cells. Together, these preliminary findings confirm the better immune status of aged women as compared to men. A detailed analysis of the datasets will identify additional correlates of sex and gender, aging, and the immune system.

The gender questionnaire implemented as part of the follow-up assessments described here will allow to calculate a gender score and its evaluation based on the newly collected clinical and psychosocial follow-up data. At the same time, the other BASE-II research foci established over the past 10 years will be continued and strengthened with the transition of BASE-II into a longitudinal study with follow-up data on the older subsample.

Other measurements

Similar to baseline, we determined numerous routine laboratory parameters from blood and urine (Table 2), and also stored blood plasma/serum and urine samples for future analyses. Genomic DNA was already extracted from EDTA-blood and buccal swab samples from GendAge participants, which will be used e.g. for the profiling of genome-wide DNA methylation signatures and new genome-wide single nucleotide polymorphism genotyping experiments (Table 2). In-between the two assessment days at the Charité, participants were asked to fill out a comprehensive psychosocial take-home questionnaire and return this at their second Charité visit.

At baseline, the BASE-II included a group of 600 younger subjects aged 20-35 years serving as a reference population [1], of which 500 completed baseline medical assessments. Between 7 February 2020 and 13 March 2020, we performed follow-up assessments in a total of 64 participants of this younger group until these assessments were suspended because of the SARS-Cov2 pandemic. These younger participants had a mean age of 36.8 years (SD ± 3.5, range 29.3 - 44.1 years), with up to 10.7 years of follow-up (minimum 6.1 years, mean follow-up at 8.2 years, SD ± 1.6). Follow-up for these younger BASE-II participants essentially followed the protocol used for the 1,100 older BASE-II participants. Because this younger group is not primarily part of the analyses planned in GendAge, further details about this group will be described elsewhere.

The cognitive session carried out by the Max Planck Institute for Human Development (MPIB) lasted about 4.5 to 5 hours (third study visit). Subjects were tested in groups of 4–6 individuals. The cognitive battery included 17 measures of learning and memory performance, attention/processing speed, working memory, executive functioning, and perceptual speed (see Table 2). Within the week between study visit 2 (Charité) and 3 (MPIB) accelerometers (ActiGraph wGT3X-BT) have been used to track participants' physical activity and sleep in a subset of our participants (N=750).

After the cognitive session, participants were invited to take part in a one-to-one interview on a different day. This additional individual assessment took up to 60 minutes and serves as a cohort comparison between the BASE and BASE-II study populations. This additional data collection will also contribute to the BASE-II cognitive waves, allowing us to further investigate individual differences in aging trajectories (for an overview, refer to[20]).

Furthermore, and as part of a collaboration with the Lifebrain study, a consortium of European studies funded by the EU Horizon 2020 Framework Programme[40], we collected blood samples using dried blood cards, in order to determine laboratory parameters with identical methods used for all Lifebrain participating sites. Lifebrain aims at identifying determinants of healthy lifespan development by integrating and harmonizing data and results from 11 large and

predominantly longitudinal European samples from 7 countries. This has yielded a database of fine-grained measures focusing on brain and cognition from more than 7,000 individual participants.

The GendAge study was approved by the Ethics Committee of the Charité–Universitätsmedizin Berlin (approval number EA2/144/16) and all participants gave written informed consent. GendAge is registered in the German Clinical Trials Register (Study-ID: DRKS00016157). The cognitive battery was approved by the Ethics Committee of the Max-Planck-Institute and the genomics experiments were approved by the Ethics Committees of the Charité (approval number EA2/144/16) and the University of Lübeck (approval numbers AZ19-390A and 19-391A).

Strengths and limitations

The BASE-II follow-up assessments covered most of the medical, psycho-social and cognitive domains and variables assessed at baseline, and thereby taking the BASE-II characteristic of an exceptionally broad and in-depth data collection to a next, longitudinal level. In addition, and in the context of the GendAge focus on cardio-metabolic disease, we extended the assessments in this area e.g. by including high-quality echocardiography resulting in a unique data collection. This strength with respect to comprehensive and longitudinal data offers the potential to answer a number of questions that are of crucial relevance for the health of old women and men. Thus, GendAge will make important contributions for improvements in understanding the health and well-being of older adults in both genders. BASE-II was initiated as a multidisciplinary study with expertise in a broad range of fields relevant for aging research (e.g. internal medicine and geriatrics, biology, psychology, genetics, immunology, socio-economics, and now in GendAge further extended by socio-cultural aspects of gender). The past ten years of BASE-II research have shown that multidisciplinary collaboration is not only a statement of intent, but a fruit-bearing working posture and a clear strength of BASE-II.

Sampling bias is a challenge which cohort studies have to deal with, and this is especially an issue in the follow-up of older study populations such as the older group of BASE-II participants. To address this, we have made a considerable effort (e.g. offering a taxi service for participants not able to travel independently) to include as many participants in the follow-up as possible. Additionally, and similar to baseline, we are able to systematically quantify the sampling bias and even account for it when it comes to the question of generalizability of study results to a population as a whole (e.g., Berlin or Germany), due to the evaluation of selectivity and representativeness via the German Socio-Economic Panel Study (SOEP) [1]. Despite these possibilities we cannot rule out the possibility of a selection bias completely, which certainly is a weakness of this study, a weakness that applies to all cohort studies relying on voluntary participants who have been non-randomly recruited. With our direct comparability to the

national representative SOEP study, we are in a position though to quantify the amount of selectivity and, if need, take measures to correct and adjust our results.

Collaboration

More details on GendAge can be found at https://gendage.charite.de/en/ and information on the BASE-II as a whole is available at https://www.base2.mpg.de/en. BASE-II has a tradition of sharing data and biobank samples in joint collaborative projects which will be continued with respect to BASE-II data assessed in GendAge. Interested groups are invited to contact the study coordinating PI Ilja Demuth at ilja.demuth@charite.de for the data-sharing application form. Each application will be reviewed by the GendAge PIs (currently ID, VRZ and DG) and the decision communicated to the applicants usually within 4 weeks of submission.

Participant and public involvement

Participants and public were not involved in the design or conduct of this study.

Funding statement

The GendAge study research project (Co-PIs are Ilja Demuth, Vera Regitz-Zagrosek, and Denis Gerstorf) is supported by the German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung, BMBF) grant numbers 01GL1716A (ID and VRZ) and 01GL1716B (DG). Genomics assessments are funded by the Cure Alzheimer's Fund (as part of the "CIRCUITS-AD" consortium project) and the European Research Council's "Horizon2020" funding scheme (as part of the "Lifebrain" consortium project; both to LB). Additional contributions (e.g., equipment, logistics, personnel) are made from each of the participating sites.

Contributorship statement

Conceived and designed the study: ID, VRZ, SD, UL and DG. Collected study specific data: I.D., VLB, JD, SD, US, DS, ET, JB, LB and AT. Providing BASE-II baseline data: DG, EST, ID, JD, LB, SD and UL. Analysed the data: ID, ET and JB. Wrote the manuscript: ID. All authors revised and approved the manuscript.

Acknowledgements

We are deeply indebted to all individuals of the BASE-II cohort who have agreed to participate in the follow-up assessments. We would further like to thank all staff members and students involved in the medical examinations of participants and documentation, especially Nora Berger, Janina Dombrowski, Mergim Domuzeti, Elisa Dreißig, Ilona Enarovic, Anthony Ganswindt, Thomas Grenkowitz, Anna Hunold, Ilias Katsianas, Yoo-Ri Kim, Jörn

Kiselev, Paula Krull, Christine Kytmannow, Elisa Lemke, Julia Mätzkow, Charlotte Mentzel, Nadja Mielke, Narantuya Mishig, Angela Motz, Eduard Nitschke, Aabi Okute, Danai Pantelakis, Sophie Poser, Johanne Spieker and Taleka Vollmar (all Charité Universitaetsmedizin Berlin, Biology of Aging group); and Luisa Lüth, Mariebelle Kaus, Isabel Ganter, Marlene Rosendahl, Jasmin Boneberger, Antonia Sprenger, Hania El-Kersh (all Humboldt University, Department of Psychology), and Kirsten Becker for the excellent daily organization of the running study within and between the research units, the Telefonstudio for their daily contact with the participants, Martin Becker for the continuous quality checks of our sample and Berndt Wischnewski for updating the database and cognitive battery (all Max Planck Institute for Human Development).

We kindly acknowledge the excellent cooperation with the Central Biomaterial Bank, the joint core facility of the Charité-Universitätsmedizin Berlin and the Berlin Institute for Health (BIH). Furthermore, we appreciate the great support by the BIH-REDCap team and especially from Andreas Hetey. We would like to acknowledge the assistance of the Charité|BIH Cytometry Core.

Conflict of interest: None declared.

Data availability statement

Data are available upon reasonable request. The GendAge study principal investigators welcome new collaborations with other investigators. Interested investigators are invited to contact the study coordinating PI Ilja Demuth at ilja.demuth@charite.de to obtain additional information about the GendAge study and the data-sharing application form.

Tables

Table 1: Selection of BASE-II follow-up characteristics as assessed of the GendAge study

	Total number of observations	Women[1] (N=573, 52.1%)	Men[1] (N=527, 47.9%)	*p-value*[2]
Age (years)	1,100	75.7 (± 3.5)	75.5 (± 4.0)	0.276
Highest school degree Elementary school Intermediate school High school	1,095	35 (6.1%) 183 (32.0%) 354 (61.9%)	18 (3.4%) 104 (19.9%) 401 (76.7%)	<0.001
Family status Married Not married, in partnership Single Divorced Widowed Other	1,098	218 (38.0%) 12 (2.1%) 60 (10.5%) 187 (32.6) 89 (15.5%) 7 (1.2%)	386 (73.5%) 19 (3.6%) 33 (6.3%) 51 (9,7%) 26 (5.0%) 10 (1.9)	<0.001
Employment status Retired	1,055	540 (97.6)	486 (96.8)	0.689
Self-rated health Very good Good Fair Poor or very poor	1,096	56 (9.8%) 284 (49.7%) 166 (29.0%) 66 (11.5%)	65 (12.4%) 262 (50.0%) 143 (27.3%) 54 (10.3%)	0.499
Satisfaction with life in general	1,097	7.9 (±1.6)	8.1 (±1.4)	<0.05
Digit Symbol Substitution Test[3]	1,095	41.37(±8.48)	39.21(±9.67)	<0.001
Verbal learning test	925	41.6 (±12.3)	44.0 (±12.8)	<0.01
Depression (ever diagnosed)	1,095	122 (21.3%)	63 (12.0%)	<0.001
BMI	1,098	26.6 (±4.7)	27.4 (±3.7)	<0.01
Physical inactive[4]	1,096	67 (11.7%)	65 (12.4%)	0.781
Diabetes mellitus type II (self-reported)	1,097	49 (8.6%)	82 (15.6%)	<0.001
Diabetes mellitus type II (diagnosed/ ADA guidelines 2019)	1,097	76 (13.3%)	109 (20.7%)	<0.01
Metabolic Syndrome (diagnosed, AHA/IDF/NHLBI criteria 2009)	1,074	252 (45.5%)	327 (62.9%)	<0.001
Hypertension	1,097	296 (51.7%)	311 (59.2%)	<0.05
Myocardial infarction	1,097	11 (1.9%)	24 (4.6%)	<0.05
Stroke	1,096	13 (2.3%)	20 (3.8%)	0.158
Peripheral artery disease	1,094	8 (1.4%)	15 (2.9%)	0.138

Morbidity index	955	1.0 (IQR 2.0)	1.0 (IQR 2.0)	0.594
Pulse wave velocity (m/s)	932	11.21 (±0.92)	11.04 (±0.91)	<0.01
Left ventricular ejection fraction (%)	773	64.12 (±6.24)	62.92 (±5.76)	<0.01
Left ventricular mass (g)	691	135.24 (±31.87)	179.76 (±38.96)	<0.001
Left ventricular mass index (g)[5]	690	78.55 (±16.83)	91.22 (±17.96)	<0.001
Left ventricular end-diastolic volume (ml)[5]	773	54.10 (±12.24)	63.67 (±13.58)	<0.001
Frailty (Fried) Not frail Pre-frail Frail	1,087	 260 (45.4%) 280 (48.9%) 28 (4.9%)	 251 (47.6%) 248 (47.1%) 20 (3.8%)	0.542
Maximal hand grip strength (kg)	1,098	20.5 (±4.4)	35.1 (±6.8)	<0.001
Recent thymic emigrants (naïve CD4⁺ T cells)	395[6]	64.69 (± 16.34)	51.03 (± 13.69)	<0.001
T_{EMRA} (effector memory T cells re-expressing CD45RA)	395[6]	32.82 (± 19.96)	34.94 (± 21.29)	0.309
Cytotoxic SLAMF7+ CD4⁺ T cells	181[7]	6.02 (± 5.98)	6.05 (± 6.60)	0.974

[1]Data are presented as N (%), mean ±standard deviation or median (interquartile range, IQR). [2]Differences between women and men were assessed using the parametric t test, the nonparametric Mann-Whitney U test or the $\chi 2$ where appropriate. [3]Assessed at study visit 1. [4]Assessed with the question "Are you seldom or never physically active?". [5]Adjusted for body surface area. [6]845 expected to be available after completion of the analyses. [7]629 expected to be available after completion of the analyses.

Table 2: BASE-II follow-up assessments during the two GendAge study visits and the cognitive sessions (third study visit)

Type of assessment/ domain	Example assessments/tests
Physical examination and medical history	Medical history structured by organ systems, medication, body weight, height, lifestyle (including smoking status, alcohol consumption, physical activity)
Physical status and functional tests	Tinetti Mobility Test, Timed up & Go Test, Barthel Index (ADL), Lawton Instrumental Activities of Daily Living Scale (IADL), hand grip strength, anthropometric parameters, pulse wave velocity/ arterial stiffness (Mobil-o-Graph), echocardiography, electrocardiography (ECG), spirometry, motion monitoring (Actigraph), dual-energy X-ray absorptiometry (DXA),
Psychological screening tests	Mini Mental State Examination (MMSE), Digit Symbol Substitution Test (DSST) [1], Center for Epidemiologic Studies Depression Scale (CESD)
Questionnaires	EPIC (food-frequency questionnaire), Gender Questionnaire, Pittsburgh Sleep Quality Index, Rapid Assessment of Physical Activity, SARC-F , SF-36
Laboratory values[2]	Blood, serum or plasma: 25-hydroxyvitamin D, apolipoprotein A1, apolipoprotein B, basophiles, calcium, cortisol, creatinine, creatinine kinase, C-reactive protein, cystatin C, dehydroepiandrosterone, eosinophils, erythrozytes, ferritin, folic acid, gamma-glutamyltransferase, glucose 1, glucose 2[3], glutamate, oxalacetate transaminase, glutamate-pyruvate transaminase, HbA1c, HDL-cholesterol, hematocrit, hemoglobin, homocysteine, international normalized ratio, iron, LDL-

	cholesterol, leukocytes, lipoprotein (a), lymphocytes, magnesium, MCH, MCHC, MCV, monocytes, neutrophils, oestradiol, osteocalcin, partial thromboplastin time, RDW, sex hormone-binding globulin, testosterone, thrombocytes, thyroid-stimulating hormone, thyroxine, total-cholesterol, triglycerides, triiodothyronine, urea, uric acid, vitamin B12, zinc. Urine: albumine, creatinine, desoxypyridinoline, teststrip: bilirubin, blood (erythrocytes), glucose, ketones, leukocytes, nitrite, pH value, protein, specific weight, urobilinogen Dried blood cards: arsenic, brain derived neurotropic-factor, cadmium, chromium, fatty acids (C12:0, C14:0, C15:0, C16:0, C16:1n7, C17:0, C18:0, C18:1,t6-11, C18:1,c9, C18:1,c11, C18:2,n-6, C20:0, C18:3,n-6, C18:3,n-3, C20:1,n-9, C20:2,n-6, C22:0/C20:3,n-6, C20:4,n-6, C20:5,n-3, C24:0, C22:5,n-3, C22:6,n-3, unknown), HbA1c, hsCRP, lead, mercury, nickel, total-cholesterol
Genomics	Genome-wide single nucleotide polymorphism genotyping using the “Global Screening Array” (Illumina, Inc.); genome-wide DNA methylation profiling using the “Infinium MethylationEPIC” array (Illumina, Inc.)
Psychosocial questionnaire	Well-being, positive affect and negative affect, emotion regulation, stress, personality, control beliefs, domain-specific control, time perception, embitterment, loneliness, solitude, social activities, network structure, sexuality, risk behavior, etc.

Biobanking	Blood plasma & serum, urine, DNA extracted from EDTA-blood and buccal swaps
Cognitive tests (third study visit)	*Episodic memory* (Picture-Word-Task, Face-Profession-Task, Object Location Task, Scene-Encoding, Verbal learning and memory test), *Working memory* (Letter Updating, Spatial Updating, Number-N-Back), *Executive functioning / processing speed* (Multi-Source-Interference Task, Digit Symbol Substitutions Test[1]), *Fluid intelligence* (Letter series, Number series, Practical Problems), *Subjective Health Horizon Questionnaire* (SHH-Q)
Immunological assessment	Cryopreservation of whole blood (SmartTube system) or isolated PBMCs, and serum samples. Direct ex vivo staining of recent thymic emigrants (RTE, CD31+ CD45RA+ CD4+ T cells), TEMRA (CD45RA+ CD8+ T cells), Tregs (CD25bright CD127- CD4+ T cells), cytotoxic CD4+ Tcells, amongst others using four different panels: 1) ImmunoCount Panel (CD45, CD3, CD56, CD19, CD16, CD14, CD123, CD1c); 2) RTE panel (CD3, CD4, CD8, CD45RA, CCR7, CD31, CD95, CD11a); 3) TREG panel (CD3, CD4, CD8, CD25, CD127); 4) Effector T cell panel (CD3, CD4, CD8, CD45RA, CCR7, SLAM-F7, IL-6R, CD57, PD-1). Panels were measured on MacsQuant 10 (Miltenyi), MacsQuant 16 (Miltenyi) or LSR II (BD)

[1]assessed at study visit 1 and 3, [2]blood samples were drawn after a fasting period of at least 8 hours (if not otherwise indicated), [3]post-load (75g glucose, 2h), not assessed in participants with known diabetes

Figure Legend:

Figure 1: Flow chart explaining the final BASE-II sample with follow-up assessments completed in GendAge

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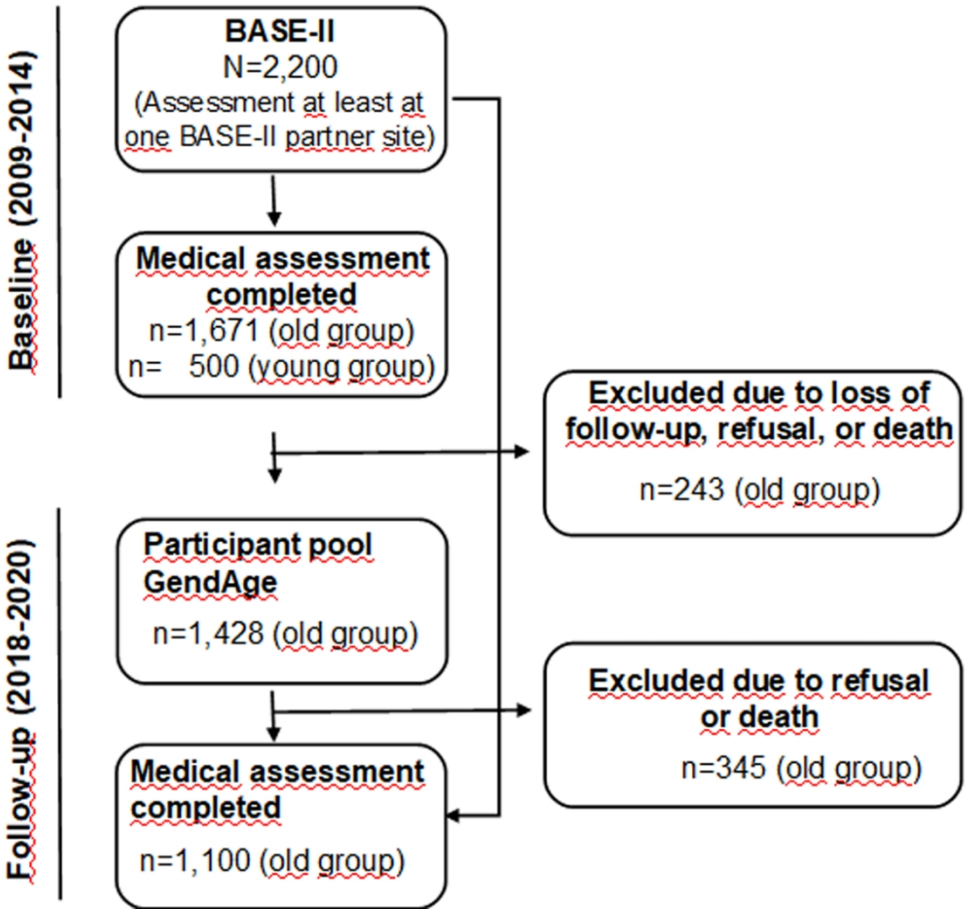

Figure 1: Flow chart explaining the final BASE-II sample with follow-up assessments completed in GendAge

99x90mm (300 x 300 DPI)